10/531,877

STN Structure Search 9/7/06

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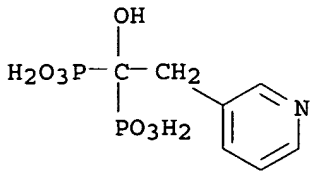
L3 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:114482 CAPLUS
DOCUMENT NUMBER: 144:239571
TITLE: The role of TG/DTA in the initial evaluation of the solid state forms for pharmaceutical new chemical entities part II: evaluation of mixed forms
AUTHOR(S): Collins, Wendy J.; Dicks, Michael L.; Redman-Furey, Nancy L.; Godlewski, Jane; Vaughn, Dana C.
CORPORATE SOURCE: P+G Pharmaceuticals, Inc., Norwich, NY, 13815, USA
SOURCE: Proceedings of the NATAS Annual Conference on Thermal Analysis and Applications (2003), 31st, 090/1-090/8
CODEN: PNACCS
PUBLISHER: NATAS
DOCUMENT TYPE: Journal; (computer optical disk)
LANGUAGE: English

AB TG/DTA plays a central role in the strategy outlined for early evaluation of the solid state forms available to pharmaceutical new chemical entities. At this stage of development, compound and time are often at a premium so a successful strategy requires making the best possible use of the materials and time available. In addition, because of time and compound limitations, the goal of the solid state investigation at this stage focuses upon early stage objectives rather than development of a complete understanding of all available solid state forms. Examples of the test strategies developed in the authors' laboratory are provided. When mixed forms were present within individual samples, TG/DTA in combination with light microscopy and powder X-ray diffraction provided evidence that samples represented mixed solid state forms. The initial assessment was made using as little as 5 mg of sample. Hygroscopicity challenges provided further proof for mixed forms. To make a definite assignment of the solid state forms present, isolation of pure phases of the suspected individual forms was necessary. Success of the testing strategy is illustrated using an example of mixed salt stoichiometry and mixed hydration states. A hierarchy is suggested for efficient isolation efforts when a complex mixture of solid state samples is present. Use of this strategy demonstrates the ability of TG/DTA in combination with XRPD and hygroscopicity studies to unequivocally identify solid state forms within a complex mixture

IT 353228-19-0, Risedronate sodium hydrate
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(TG/DTA combined with light microscopy and XRPD enabled early detection of solid state mixed forms and provided information regarding nature and level of hydration of risedronate like monosodium monohydrate, hemi-pentahydrate and free acid)

RN 353228-19-0 CAPLUS
CN Phosphonic acid, [1-hydroxy-2-(3-pyridinyl)ethylidene]bis-, monosodium salt, monohydrate (9CI) (CA INDEX NAME)



● Na

● H_2O

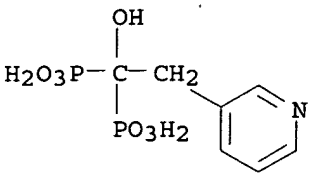
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1174909 CAPLUS
DOCUMENT NUMBER: 144:280250
TITLE: The role of TGA-DTA in the initial evaluation of the solid state forms for pharmaceutical new chemical entities, part 2: Evaluation of mixed forms
AUTHOR(S): Redman-Furey, Nancy L.; Dicks, Michael L.; Godlweski, Jane; Vaughn, Dana C.; Collins, Wendy J.
CORPORATE SOURCE: P and G Pharmaceuticals, Inc., Norwich, NY, 13815, USA
SOURCE: Journal of ASTM International (2005), 2(1), No pp. given
CODEN: JAIOAD
URL: http://journalsip.astm.org/DOWNLOAD/JAI12792.27924-1.pdf
PUBLISHER: ASTM International
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English

AB TGA-DTA plays a central role in the strategy outlined for early evaluation of the solid state forms available to pharmaceutical new chemical entities. Understanding of the solid state forms becomes more difficult when individual samples present as mixed forms, especially when it is not immediately recognized that the samples represent a mixture In this study, TGA-DTA, in combination with light microscopy and powder X-ray diffraction, provided immediate evidence that samples represented mixed solid state forms. The initial assessment was made using as little as 5 mg of sample. Hygroscopicity challenges provided further proof for mixed forms. To make a definite assignment of the solid state forms present, isolation of pure phases of the suspected individual forms was necessary. Success of this testing strategy is illustrated using an example of mixed salt stoichiometry and mixed hydration states. A hierarchy is suggested for efficient isolation efforts when a complex mixture of solid state samples is present.

IT 353228-19-0
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(TGA-DTA detected presence of channel and lattice hydrate types, their inter-conversion and mixed solid state forms for Risedronate suggesting its utility in evaluation of solid state forms for pharmaceutical new chemical entity)
RN 353228-19-0 CAPLUS

CN Phosphonic acid, [1-hydroxy-2-(3-pyridinyl)ethylidene]bis-, monosodium salt, monohydrate (9CI) (CA INDEX NAME)



● Na

● H_2O

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:300227 CAPLUS
DOCUMENT NUMBER: 142:341951
TITLE: Pharmaceutical formulation of bisphophonates with improved stability
INVENTOR(S): Lulla, Amar; Malhotra, Geena
PATENT ASSIGNEE(S): Cipla Limited, India; Wain, Christopher Paul
SOURCE: PCT Int. Appl., 20 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005030177	A2	20050407	WO 2004-GB4146	20040929
WO 2005030177	A3	20051222		
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RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2004275569	A1	20050407	AU 2004-275569	20040929
CA 2540488	AA	20050407	CA 2004-2540488	20040929
EP 1680092	A2	20060719	EP 2004-768689	20040929
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR				

PRIORITY APPLN. INFO.: IN 2003-MU1023 A 20030929
WO 2004-GB4146 W 20040929

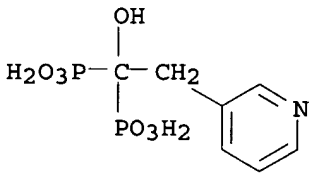
AB There is provided an oral formulation which includes an intragranular phase comprising a bisphosphonic acid derivative and at least one carbohydrate

alc., together with an aqueous binder. There are also provided a process of preparing the same and a therapeutic method employing such a formulation in the treatment of various skeletal diseases, such as systemic bone diseases including osteoporosis, osteoarthritis, Paget's disease, osteomalacia, multiple myeloma, and other forms of cancer, steroid therapy wherein the skeletal system is effected and age-related loss of bone mass, local disorders such as bone fractures and other such related disorders. For example, tablets were formulated containing alendronate Na trihydrate 35, microcryst. cellulose 57.5, mannitol 58.32, starch 1.5, Mg stearate 2, and Na starch glycollate 8.9 mg.

IT 353228-19-0
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral compns. containing intragranular phase of bisphosphonate and sugar alcs.)

RN 353228-19-0 CAPLUS

CN Phosphonic acid, [1-hydroxy-2-(3-pyridinyl)ethylidene]bis-, monosodium salt, monohydrate (9CI) (CA INDEX NAME)



● Na

● H_2O

L3 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2001:581839 CAPLUS
DOCUMENT NUMBER: 135:157693
TITLE: Selective crystallization of 3-pyridinyl-1-hydroxyethylidene-1,1-bisphosphonic acid sodium as the hemipentahydrate or monohydrate
INVENTOR(S): Cazer, Fredrick Dana; Perry, Gregory Eugene; Billings, Dennis Michael; Redman-Furey, Nancy Lee
PATENT ASSIGNEE(S): Procter + Gamble Company, USA
SOURCE: PCT Int. Appl., 12 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001056983	A2	20010809	WO 2001-US3336	20010201
WO 2001056983	A3	20020307		

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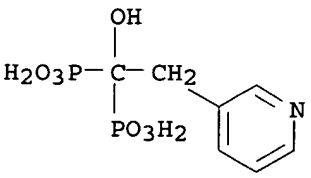
	ZA, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US	2002002282	A1	20020103	US 2001-771825	20010129
US	6410520	B2	20020625		
CA	2399976	AA	20010809	CA 2001-2399976	20010201
AU	2001034736	A5	20010814	AU 2001-34736	20010201
AU	784307	B2	20060309		
BR	2001007921	A	20021022	BR 2001-7921	20010201
EP	1252170	A2	20021030	EP 2001-906880	20010201
EP	1252170	B1	20040818		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP	2003521532	T2	20030715	JP 2001-556833	20010201
NZ	519966	A	20040326	NZ 2001-519966	20010201
AT	273984	E	20040915	AT 2001-906880	20010201
RU	2236415	C2	20040920	RU 2002-123369	20010201
PT	1252170	T	20041231	PT 2001-906880	20010201
ES	2225481	T3	20050316	ES 2001-1906880	20010201
ZA	2002005090	A	20030207	ZA 2002-5090	20020625
NO	2002003645	A	20021001	NO 2002-3645	20020731
HK	1051046	A1	20050429	HK 2003-101833	20030313
PRIORITY APPLN. INFO.:				US 2000-179505P P	20000201
				WO 2001-US3336 W	20010201

AB The present invention discloses 3-pyridinyl-1-hydroxyethylidene-1,1-bisphosphonic acid sodium hemipentahydrate and monohydrate, (risedronate sodium hydrates) methods of preparing the hemipentahydrate or monohydrate through control of the nucleation temperature and rate of crystallization and pharmaceutical compns. containing 1 or both of the hydrate forms. An aqueous solution of risedronate sodium selective yields the monohydrate or the hemipentahydrate crystal forms depending upon the conditions of crystallization The temperature of nucleation and the rate of crystallization govern the hydrate, varying the ratio of water-iso-PrOH and the temperature

IT 353228-19-0P
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(selective crystallization of pyridylhydroxyethylidenebisphosphonate as hydrates)

RN 353228-19-0 CAPLUS

CN Phosphonic acid, [1-hydroxy-2-(3-pyridinyl)ethylidene]bis-, monosodium salt, monohydrate (9CI) (CA INDEX NAME)



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● H_2O

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L2           1 S E2

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L3           4 S L2

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L2   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2006 ACS on STN
RN   353228-19-0  REGISTRY
ED   Entered STN:  28 Aug 2001
CN   Phosphonic acid, [1-hydroxy-2-(3-pyridinyl)ethylidene]bis-, monosodium
     salt, monohydrate (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   Risedronate sodium hydrate
MF   C7 H11 N O7 P2 . H2 O . Na
SR   CA
LC   STN Files:   CA, CAPLUS, IMSPATENTS, USPAT2, USPATFULL
CRN  (105462-24-6)
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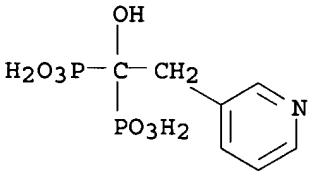

● Na

● H_2O

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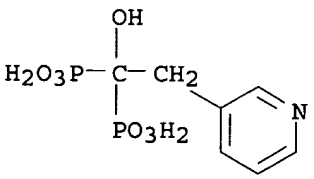
L6   ANSWER 1 OF 9  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:        2006:114482  CAPLUS
DOCUMENT NUMBER:         144:239571
TITLE:                   The role of TG/DTA in the initial evaluation of the
                         solid state forms for pharmaceutical new chemical
                         entities part II: evaluation of mixed forms
AUTHOR(S):               Collins, Wendy J.; Dicks, Michael L.; Redman-Furey,
```

Nancy L.; Godlewski, Jane; Vaughn, Dana C.
CORPORATE SOURCE: P+G Pharmaceuticals, Inc., Norwich, NY, 13815, USA
SOURCE: Proceedings of the NATAS Annual Conference on Thermal Analysis and Applications (2003), 31st, 090/1-090/8
CODEN: PNACCS
PUBLISHER: NATAS
DOCUMENT TYPE: Journal; (computer optical disk)
LANGUAGE: English
AB TG/DTA plays a central role in the strategy outlined for early evaluation of the solid state forms available to pharmaceutical new chemical entities. At this stage of development, compound and time are often at a premium so a successful strategy requires making the best possible use of the materials and time available. In addition, because of time and compound limitations, the goal of the solid state investigation at this stage focuses upon early stage objectives rather than development of a complete understanding of all available solid state forms. Examples of the test strategies developed in the authors' laboratory are provided. When mixed forms were present within individual samples, TG/DTA in combination with light microscopy and powder X-ray diffraction provided evidence that samples represented mixed solid state forms. The initial assessment was made using as little as 5 mg of sample. Hygroscopicity challenges provided further proof for mixed forms. To make a definite assignment of the solid state forms present, isolation of pure phases of the suspected individual forms was necessary. Success of the testing strategy is illustrated using an example of mixed salt stoichiometry and mixed hydration states. A hierarchy is suggested for efficient isolation efforts when a complex mixture of solid state samples is present. Use of this strategy demonstrates the ability of TG/DTA in combination with XRPD and hygroscopicity studies to unequivocally identify solid state forms within a complex mixture

IT 115436-72-1, Risedronate Sodium
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(TG/DTA combined with light microscopy and XRPD enabled early detection of solid state mixed forms and provided information regarding nature and level of hydration of risedronate like monosodium monohydrate, hemi-pentahydrate and free acid)

RN 115436-72-1 CAPLUS
CN Phosphonic acid, [1-hydroxy-2-(3-pyridinyl)ethylidene]bis-, monosodium salt (9CI) (CA INDEX NAME)

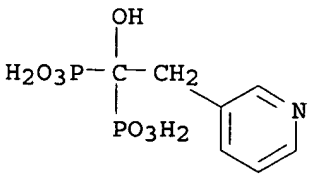


● Na

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:96118 CAPLUS
DOCUMENT NUMBER: 144:419282
TITLE: Monitoring hydration state conversion by TGA-DTA
AUTHOR(S): Poiesz, Kate B.; Grundner, Carol L.; Redman-Furey,

Nancy L.
CORPORATE SOURCE: Procter & Gamble Pharmaceuticals, Inc., Norwich, NY, 13815, USA
SOURCE: Proceedings of the NATAS Annual Conference on Thermal Analysis and Applications (2005), 33rd, 105.37.255/1-105.37.255/10
CODEN: PNACCS
PUBLISHER: NATAS
DOCUMENT TYPE: Journal; (computer optical disk)
LANGUAGE: English
AB Active pharmaceutical ingredients may crystallize in different polymorphic and/or hydration states. Differing solid state forms may express variation in key properties that impact performance attributes such as solubility, dissoln. rate, and stability. Depending upon formulation needs, the thermodynamically most stable form may not be chosen for manufacture of the final drug product. Under these circumstances, it is important to understand the relative stability of the metastable form under anticipated long-term storage conditions. Hydrates require an addnl. level of concern in regards to potential phase changes. Like polymorphs, the concern exists for a change in property, such as solubility (and subsequent altering of dissoln. rate), upon change in hydrate form. But unlike polymorphic changes, a change in hydration state may also result in release of water into a formulation (change to lower hydration state) or the robbing of available water from a formulation (change to a higher hydration level). Changes in water distribution within a formulation may result in unexpected changes in tablet hardness or ability to release, cause capsule brittleness, or decrease formulation stability. Understanding the parameters necessary for long-term maintenance of a metastable hydrate is clearly of importance to the design of a stable formulation. TGA-DTA is an effective tool for monitoring changes in hydration state. TGA-DTA can quantitate total water content and illustrate hydrate type in a single experiment with only a few milligrams of sample. KF, LOD, or NIRA can monitor water content but not identify phase. XRD may be used to assess hydrate type but is not necessarily quant. Solid State NMR may identify phase and quantitate water content but requires an order of magnitude more sample and a training set of samples to establish a calibration curve.
IT 115436-72-1, Risedronate sodium
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(monitoring hydration state conversion by TGA-DTA)
RN 115436-72-1 CAPLUS
CN Phosphonic acid, [1-hydroxy-2-(3-pyridinyl)ethylidene]bis-, monosodium salt (9CI) (CA INDEX NAME)



● Na

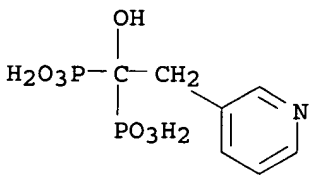
REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 3 OF 9 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:1174909 CAPLUS
DOCUMENT NUMBER: 144:280250
TITLE: The role of TGA-DTA in the initial evaluation of the solid state forms for pharmaceutical new chemical entities, part 2: Evaluation of mixed forms
AUTHOR(S): Redman-Furey, Nancy L.; Dicks, Michael L.; Godlweski, Jane; Vaughn, Dana C.; Collins, Wendy J.
CORPORATE SOURCE: P and G Pharmaceuticals, Inc., Norwich, NY, 13815, USA
SOURCE: Journal of ASTM International (2005), 2(1), No pp. given
CODEN: JAIOAD
URL: http://journalsip.astm.org/DOWNLOAD/JAI12792.27924-1.pdf
PUBLISHER: ASTM International
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English

AB TGA-DTA plays a central role in the strategy outlined for early evaluation of the solid state forms available to pharmaceutical new chemical entities. Understanding of the solid state forms becomes more difficult when individual samples present as mixed forms, especially when it is not immediately recognized that the samples represent a mixture In this study, TGA-DTA, in combination with light microscopy and powder X-ray diffraction, provided immediate evidence that samples represented mixed solid state forms. The initial assessment was made using as little as 5 mg of sample. Hygroscopicity challenges provided further proof for mixed forms. To make a definite assignment of the solid state forms present, isolation of pure phases of the suspected individual forms was necessary. Success of this testing strategy is illustrated using an example of mixed salt stoichiometry and mixed hydration states. A hierarchy is suggested for efficient isolation efforts when a complex mixture of solid state samples is present.

IT 115436-72-1, Risedronate sodium
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(TGA-DTA detected presence of channel and lattice hydrate types, their inter-conversion and mixed solid state forms for Risedronate suggesting its utility in evaluation of solid state forms for pharmaceutical new chemical entity)
RN 115436-72-1 CAPLUS
CN Phosphonic acid, [1-hydroxy-2-(3-pyridinyl)ethylidene]bis-, monosodium salt (9CI) (CA INDEX NAME)



● Na

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:823715 CAPLUS
DOCUMENT NUMBER: 143:212018

10/531,877

TITLE: Preparation of stable crystalline form of monosodium risedronate hydrate
INVENTOR(S): Richter, Jindrich; Jirman, Josef
PATENT ASSIGNEE(S): Zentiva, A.S., Czech Rep.
SOURCE: PCT Int. Appl., 14 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005075487	A1	20050818	WO 2005-CZ12	20050204

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
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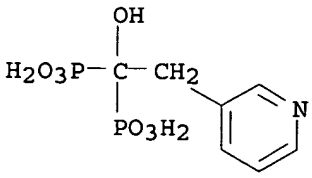
PRIORITY APPLN. INFO.: CZ 2004-199 A 20040205

AB Stable crystalline modification of monosodium 3-pyridyl-1-hydroxyethylidene-1,1-bisphosphonate hydrate (monosodium risedronate J form), useful in treatment of bone diseases and to adjust calcium metabolism (no data) was prepared by heating of the metastable H form at 50° for 3-10 h. The new modification is characterized by its x-ray pattern with characteristic interplanar distances 4.35; 8.44; 13.42 and 15.73 u and was found to be stable at room temperature for 9 mo in a sealed glass container.

IT 115436-72-1P, Risedronic acid monosodium salt
RL: SPN (Synthetic preparation); PREP (Preparation)
(crystalline modification; preparation of stable crystalline modification of monosodium 3-pyridinyl 1-hydroxyethylidene 1,1-bisphosphonate hydrate)

RN 115436-72-1 CAPLUS
CN Phosphonic acid, [1-hydroxy-2-(3-pyridinyl)ethylidene]bis-, monosodium salt (9CI) (CA INDEX NAME)



● Na

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:314094 CAPLUS
DOCUMENT NUMBER: 143:292160

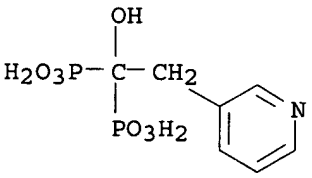
10/531,877

TITLE: Structural and analytical characterization of three hydrates and an anhydrate form of risedronate
AUTHOR(S): Redman-Furey, Nancy; Dicks, Michael; Bigalow-Kern, Adrienne; Cambron, R. Thomas; Lubey, Gwen; Lester, Cathy; Vaughn, Dana
CORPORATE SOURCE: Procter and Gamble Pharmaceuticals, Inc., Norwich, NY, 13815, USA
SOURCE: Journal of Pharmaceutical Sciences (2005), 94(4), 893-911
CODEN: JPMSAE; ISSN: 0022-3549
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Four hydration states are reported for Risedronate monosodium. A single-crystal x-ray structure determination is provided as proof of assignment for the monohydrate, hemi-pentahydrate, and variable hydrate forms. The structure provided for the anhydrate form was determined through simulating annealing calcns. and subsequent Reitveld refinement of a high-quality x-ray powder diffraction patterns Favorable comparisons of exptl. obtained x-ray powder patterns are made to those generated from the single crystal data. Characteristic IR, Raman, and NMR spectra are provided and discussed for each form as are thermal anal. profiles. In addition, photomicrographs are provided for each of the forms isolated for this study. The hemi-pentahydrate is demonstrated to be the equilibrium form at room temperature and 37°, in the presence of water.

IT 115436-72-1, Risedronate sodium
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(structural and anal. characterization of three hydrates and an anhydrate form of risedronate)

RN 115436-72-1 CAPLUS
CN Phosphonic acid, [1-hydroxy-2-(3-pyridinyl)ethylidene]bis-, monosodium salt (9CI) (CA INDEX NAME)



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REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

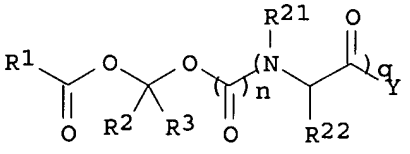
L6 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:717749 CAPLUS
DOCUMENT NUMBER: 139:245676
TITLE: Methods for synthesis of 1-(acyloxy)alkyl carbamates and analogs as prodrugs from 1-acylalkyl derivatives and compositions thereof
INVENTOR(S): Gallop, Mark A.; Xiang, Jia-Ning; Yao, Fenmei; Bhat, Laxminarayan; Zhou, Cindy X.
PATENT ASSIGNEE(S): Xero Port, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 34 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003171303	A1	20030911	US 2002-167797	20020611
US 6927036	B2	20050809		
WO 2003077902	A1	20030925	WO 2002-US18691	20020611
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002316231	A1	20030929	AU 2002-316231	20020611
EP 1485082	A1	20041215	EP 2002-746514	20020611
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2005239725	A1	20051027	US 2005-158405	20050621

PRIORITY APPLN. INFO.:	US 2002-358603P	P	20020219
	US 2002-371535P	P	20020409
	US 2002-167797	A3	20020611
	WO 2002-US18691	W	20020611

OTHER SOURCE(S): CASREACT 139:245676; MARPAT 139:245676
GI



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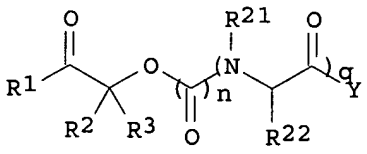

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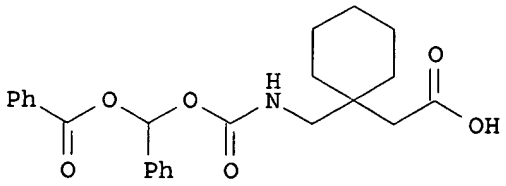


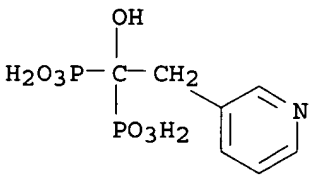
III

AB The present invention provides a method for synthesizing 1-(acyloxy)alkyl derivs. I from 1-acylalkyl derivs. II [wherein n = 0-1; q = 0-1; provided that n and q = 0 unless Y = NRR' or OR; Y = NRR', OR, COR, PO(OR')R, or PO(OR')(OR); NRR', OR, COR, PO(OR')R, or PO(OR')(OR) = groups derived from drugs containing the indicated functional groups, with provisos; R1 = H or (un)substituted alkyl, (hetero)cycloalkyl, (hetero)arylalkyl, or a C23 bile acid moiety; R2 and R3 = independently H or (un)substituted (cyclo)alkyl, (cyclo)alkoxycarbonyl, aryl(alkyl), carbamoyl, or heteroaryl(alkyl); or R1 and either R2 or R3 may join together with the atoms to which they are attached to form an (un)substituted (hetero)cycloalkyl ring optionally fused to a (hetero)aryl or (hetero)cycloalkyl ring; or CR2R3 = (un)substituted (hetero)cycloalkyl; R21 = independently H or (un)substituted alkyl; R22 = independently H or

(un)substituted (cyclo)alkyl, alkoxy(carbonyl), acyl, alkylamino, alkylthio, carbamoyl, aryl(alkyl), heteroaryl(alkyl), etc.; or pharmaceutically acceptable slats, hydrates, or solvates thereof]. The method typically proceeds stereospecifically, in high yield, does not require the use of activated intermediates and/or toxic compds., and is readily amenable to scale-up. The invention also provides 1-acylalkyl derivs. of known drug compds. and methods for synthesizing these 1-acylalkyl derivs. I and compns. thereof are useful as prodrugs (no data). For example, coupling of benzoin with p-nitrophenyl chloroformate using DMAP in CH2Cl2, followed by the addition of gabapentin in the presence of TEA and TMSCl CH2Cl2 gave 1-[[(α-benzoylbenzyloxy)carbonyl]aminomethyl]-1-cyclohexaneacetic acid (90% over two steps). Oxidation with mCPBA in CH2Cl2 provided the α-(benzoyloxy)benzyl carbamate III (47%).

IT 115436-72-1DP, NE 58095, prodrug derivative
RL: IMF (Industrial manufacture); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of alkoxyalkyl carbamates and analogs as prodrugs by oxidation of acylalkyl derivs.)

RN 115436-72-1 CAPLUS
CN Phosphonic acid, [1-hydroxy-2-(3-pyridinyl)ethylidene]bis-, monosodium salt (9CI) (CA INDEX NAME)



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REFERENCE COUNT: 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:252364 CAPLUS
DOCUMENT NUMBER: 139:202652
TITLE: Thermoanalytical characterization of the hydration states of risedronate
AUTHOR(S): Redman-Furey, Nancy L.; Collins, Wendy J.; Burgin, Matthew A.
CORPORATE SOURCE: Procter & Gamble Pharmaceuticals, Inc., Norwich, NY, 13464, USA
SOURCE: Proceedings of the NATAS Annual Conference on Thermal Analysis and Applications (2002), 30th, 733-738
CODEN: PNACCS
PUBLISHER: NATAS
DOCUMENT TYPE: Journal
LANGUAGE: English

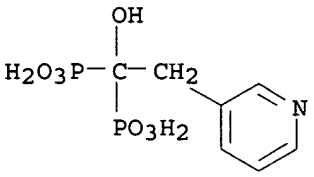
AB Risedronate, the active pharmaceutical ingredient in Actonel, is manufactured as the hemi-pentahydrate. In addition to the hemi-pentahydrate, monohydrate and anhydrate forms of the drug were isolated. Each of these hydrate forms displayed a unique thermoanal. signature by both TGA and DSC. The appearance of the TGA and DSC thermal curves for the hemi-pentahydrate form is highly dependent upon exptl. parameters such as scan rate and sample pan venting. Most of this dependence can be

explained by the channel nature of a portion of the water of hydration of the hemi-pentahydrate and the fact that under some conditions, a conversion from hemi-pentahydrate to monohydrate occurred during the thermoanal. experiment

IT 115436-72-1, Actonel
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(thermoanal. characterization of hydration states of risedronate)

RN 115436-72-1 CAPLUS

CN Phosphonic acid, [1-hydroxy-2-(3-pyridinyl)ethylidene]bis-, monosodium salt (9CI) (CA INDEX NAME)



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REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

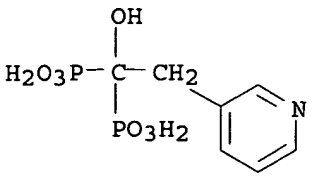
L6 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:791345 CAPLUS
DOCUMENT NUMBER: 138:162724
TITLE: Sodium risedronate hydrate
AUTHOR(S): Kushida, Kazuhiro
CORPORATE SOURCE: Dep. Orthopaedic Surg., Hamamatsu Univ. Sch. Med., Japan
SOURCE: Rinsho to Yakubutsu Chiryo (2002), 21(10), 1040-1041
CODEN: RYCHEI; ISSN: 0913-7505
PUBLISHER: Eruzebia-Saiensu K.K. Mikusu
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese

AB A review. After comparing sodium risedronate hydrate, a drug for treatment of osteoporosis, with existing analogs, the knack of its usage and precaution against its side effects were briefly discussed.

IT 115436-72-1
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sodium risedronate hydrate for treatment of osteoporosis)

RN 115436-72-1 CAPLUS

CN Phosphonic acid, [1-hydroxy-2-(3-pyridinyl)ethylidene]bis-, monosodium salt (9CI) (CA INDEX NAME)



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L6 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:581839 CAPLUS
DOCUMENT NUMBER: 135:157693
TITLE: Selective crystallization of 3-pyridinyl-1-hydroxyethylidene-1,1-bisphosphonic acid sodium as the hemipentahydrate or monohydrate
INVENTOR(S): Cazer, Fredrick Dana; Perry, Gregory Eugene; Billings, Dennis Michael; Redman-Furey, Nancy Lee
PATENT ASSIGNEE(S): Procter + Gamble Company, USA
SOURCE: PCT Int. Appl., 12 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001056983	A2	20010809	WO 2001-US3336	20010201
WO 2001056983	A3	20020307		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002002282	A1	20020103	US 2001-771825	20010129
US 6410520	B2	20020625		
CA 2399976	AA	20010809	CA 2001-2399976	20010201
AU 2001034736	A5	20010814	AU 2001-34736	20010201
AU 784307	B2	20060309		
BR 2001007921	A	20021022	BR 2001-7921	20010201
EP 1252170	A2	20021030	EP 2001-906880	20010201
EP 1252170	B1	20040818		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003521532	T2	20030715	JP 2001-556833	20010201
NZ 519966	A	20040326	NZ 2001-519966	20010201
AT 273984	E	20040915	AT 2001-906880	20010201
RU 2236415	C2	20040920	RU 2002-123369	20010201
PT 1252170	T	20041231	PT 2001-906880	20010201
ES 2225481	T3	20050316	ES 2001-1906880	20010201
ZA 2002005090	A	20030207	ZA 2002-5090	20020625
NO 2002003645	A	20021001	NO 2002-3645	20020731
HK 1051046	A1	20050429	HK 2003-101833	20030313

10/531,877

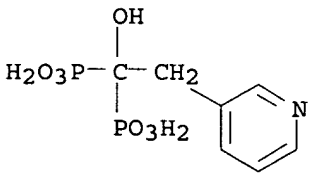
PRIORITY APPLN. INFO.: US 2000-179505P P 20000201
WO 2001-US3336 W 20010201

AB The present invention discloses 3-pyridinyl-1-hydroxyethylidene-1,1-bisphosphonic acid sodium hemipentahydrate and monohydrate, (risedronate sodium hydrates) methods of preparing the hemipentahydrate or monohydrate through control of the nucleation temperature and rate of crystallization and pharmaceutical compns. containing 1 or both of the hydrate forms. An aqueous solution of risedronate sodium selective yields the monohydrate or the hemipentahydrate crystal forms depending upon the conditions of crystallization The temperature of nucleation and the rate of crystallization govern the hydrate, varying the ratio of water-iso-PrOH and the temperature

IT 115436-72-1, Risedronate sodium
RL: RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(selective crystallization of pyridylhydroxyethylidenebisphosphonate as hydrates)

RN 115436-72-1 CAPLUS

CN Phosphonic acid, [1-hydroxy-2-(3-pyridinyl)ethylidene]bis-, monosodium salt (9CI) (CA INDEX NAME)



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L1 1 S E5
L2 1 S E2

FILE 'CAPLUS' ENTERED AT 10:50:42 ON 07 SEP 2006
L3 4 S L2

FILE 'REGISTRY' ENTERED AT 10:51:33 ON 07 SEP 2006

FILE 'CAPLUS' ENTERED AT 10:51:34 ON 07 SEP 2006
L4 81 S L1
L5 149996 S HYDRATE?
L6 9 S L4 AND L5

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